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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

009406

APR 3 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Review of 4-hour, Acute Inhalation Toxicity Study
with Benzyl Benzoate in Rats

Tox. Chem. No.: 082
HED PROJECT NO.: 2-0373A
I.D. NO.: 059820-E
MRID NO.: 418818-01

FROM: Brian Dementi, Ph.D., D.A.B.T.
Review Section III
Toxicology Branch-I
Health Effects Division (H7509C)

Brian Dementi 3/30/92

TO: Richard Mountfort
PM Team #10
Insecticide Rodenticide Branch
Registration Division (H7505C)

THRU: Henry Spencer, Ph.D.
Acting Section Head, Review Section III
Toxicology Branch I
Health Effects Division (H7509C)

HS 3/30/92 *KB 4/3/92*

Action Requested:

The Registrant has submitted a 4-hour acute inhalation study with benzyl benzoate in the rat for review toward satisfying Section 81-3 of the testing guidelines.

Conclusions

The study has been reviewed by an HED contractor and secondarily within Toxicology Branch I. The study is considered adequate to satisfying the guideline requirement for acute inhalational testing and is classified core minimum.

The finding in this study was that the acute 4-hour inhalation LC₅₀ of benzyl benzoate in male and female rats exceeds 5.02 mg/L, where the limit dose for this guideline testing requirement is 5.0 mg/L.

The review of this study is appended.

DOC 980159
FINAL

DATA EVALUATION REPORT

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Benzyl Benzoate

Study Type: Acute Inhalation Toxicity Study

**Study Title: 4-Hour Acute Inhalation Toxicity Study
with Benzyl Benzoate in Rats**

Prepared for:

**Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202**

Prepared by:

**Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207**

Principal Reviewer

Jessica Kidwell

3/20/92

Date

Independent Reviewer

John Liccione

3/24/92

Date

QA/QC Manager

Sharon Segal

3/20/92

Date

**Contract Number: 68D10075
Work Assignment Number: 1-45
Clement Number: 91-147
Project Officer: James E. Scott**

EPA Reviewer: Dr. Brian Dementi
Review Section III, Toxicology Branch I/HED

Brian Dementi
Signature
3/23/92
Date

EPA Section Head: Dr. Henry Spencer
Review Section III, Toxicology Branch I/HED

[Signature]
Signature
3/23/92
Date

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DATA EVALUATION REPORT

STUDY TYPE: Acute inhalation toxicity study

EPA IDENTIFICATION NUMBERS

Tox. Chem. Number: 082
HRID Number: 418818-01

TEST MATERIAL: Benzyl benzoate

COMMERCIAL/FINANCIAL INFORMATION IS NOT INCLUDED

SYNONYMS: [REDACTED]

SPONSOR: Werner & Mertz GmbH, Division of Environmental Medicine,
Ingelheimstrasse 1-3, D-6500 Mainz

STUDY NUMBER: 282508

TESTING FACILITY: Research and Consulting Company AG, 1, Route de Troinex,
CH-1227 Carouge, Geneva, Switzerland

TITLE OF REPORT: 4-Hour, Acute Inhalation Toxicity Study with Benzyl Benzoate
in Rats

AUTHORS: Dr. F. Duchosal, Dr. O. Vogel, Dr. H. Chevalier, and K. Biedermann

STUDY COMPLETED: December 4, 1990

CONCLUSIONS: The acute 4-hour inhalation LC₅₀ of benzyl benzoate in male and
female rats is greater than 5.02 mg/L.

CORE CLASSIFICATION: Core Minimum. This study was classified as Core Minimum
because temperature and humidity were not recorded at least every 30 minutes
during exposure and the relative humidity was not maintained between 40-60%.
No explanation for these deficiencies was provided.

TOXICITY CATEGORY: III--Caution

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A. MATERIALS

1. Test Material

Test material: Benzyl benzoate
Purity: 99% (sponsor analysis)
Physical description: Clear colorless liquid
Lot number: 51603
Storage: At room temperature (<40°C), in the original container, protected from light (sponsor analysis).
Stability: One year under storage conditions

2. Controls

Materials: None necessary
Animals: None necessary

3. Test Animals

Species: Rats
Strain: Wistar, Han-Ibm (outbred), SPF quality
Sex: Male and female
Source: BRL, Biological Research Laboratories Ltd., Fuillinsdorf, Switzerland
Receipt date: Not reported
Numbers: Five males, five females
Housing: Five/cage
Age (at delivery): 8-10 weeks
Weight: 180.4-200.0 g
Feeding: Feed and water provided ad libitum
Selection: Computer-generated randomization

4. Exposure

Route of administration: Inhalation (nose only)
Dose level: 5.02 mg/L (five male/five female)

B. TEST PERFORMANCE

Inhalation chamber

The animals were confined separately in tubes positioned radially around the exposure chamber. The flow-past, nose-only design of this exposure system was developed based upon the fluid dynamic modeling of the aerosol flow from the entry to the animal's nose. The internal active volume of the chamber for exposing 40 animals by nose-only is 1 liter. The resulting time for the concentration at an animal's port to reach 99% of its ultimate value (T99) is 34 seconds for the 40 animal chambers. The test article stream reaches the animal's nose through ports situated at different levels around the axis of the exposure chamber. Each level has eight ports and can be rotated, allowing close observation of all animals without interruption of exposure. The system is unique in comparison with conventional nose-only exposure systems in that it ensures a uniform distribution of the test article at all chamber levels, provides a constant stream of fresh test article to each animal, and precludes

rebreathing of the exhaled air. A diagram of the exposure system was provided.

The test article was placed in an automatic syringe pump feeding a nebulizer. The test atmosphere generated by the nebulizer was then diluted with clean air to achieve the concentration required for this study with a mass median aerodynamic diameter of 3 μ m or less and discharged into the exposure chamber.

Concentration and Monitoring

Five male and five female rats were exposed (nose only) for a single continuous 4-hour period to a mean concentration of 5.02 mg benzyl benzoate/L air. Concentration, particle size distribution, oxygen concentration, relative humidity, and temperature were measured on test atmosphere samples taken at the site of each animal's snout in the exposure system. All the measurements were taken directly from the test atmosphere feed tube on the flow-past exposure system that delivers fresh test article to the animal's nose. All sampling was isoaxial and represented exactly what was delivered to the animal's nose. Oxygen concentration (20.9%) was measured once during exposure. The relative humidity (14.1%) and temperature (21.3°C) were determined once during exposure. Three test atmosphere samples were taken during exposure and the average analytical concentration was determined to be 5.02 \pm 0.27 mg/L. Four gravimetric determinations were performed during exposure, with the average concentration being 5.65 \pm 1.7 mg/L. The nominal concentration was determined by weighing the syringe before and after exposure and was determined to be 7.3 mg/L. Particle size was determined once during exposure (80.9% of the particles were <3 μ m). The exposure airflow rate was adjusted prior to the start of the exposure and monitored indirectly through the aerosol generation and dilution system using calibrated flow meters.

Animals were weighed prior to treatment on day 1 and then on days 8 and 15. Animals were observed for mortality and clinical signs once per hour during exposure, once after exposure on day 1, and twice daily thereafter for 2 weeks for mortality, and at least once daily thereafter for clinical signs. Necropsies were performed on all animals. The lungs, trachea, larynx, and nasal cavities were collected from all animals and processed by a histotechnician. The slides were examined by a pathologist. All abnormalities were described and reported.

C. RESULTS AND STUDY AUTHORS' CONCLUSIONS

Tables were presented for mortality, individual body weights, individual clinical signs during and after exposure, and both macroscopic and microscopic necropsy results for each animal.

No deaths occurred during exposure or during the 15-day observation period. The acute 4-hour inhalation LC₅₀ of benzyl benzoate in rats of both sexes was estimated to be greater than 5.02 mg/L.

No clinical signs were noted during or after exposure in each animal. No treatment-related effects were noted in body weights. All animals gained weight during the study. No treatment-related gross or microscopic findings were noted in any animal. The only macroscopic observations

noted were that the lungs of all animals were incompletely collapsed. No microscopic findings were noted in the lungs, larynx, trachea, or nasal cavities.

D. REVIEWERS' COMMENTS

The reviewers agree with the study authors conclusion that the acute 4-hour inhalation LC_{50} of benzyl benzoate in rats is >5.02 mg/L. Based on the results of this limit test, the Toxicity Category for benzyl benzoate is III--Caution.

This study was classified as Core Minimum because (1) the study authors reported that temperature and humidity were determined only once during exposure, however, according to the guidelines, temperature and humidity should be recorded every 30 minutes during exposure and (2) the relative humidity was not maintained between 40% and 60% (the acceptable range established in the guidelines) and no explanation for the marked deviation was provided.

E. QUALITY ASSURANCE MEASURE

A signed Quality Assurance Statement, dated 02/28/91, was presented. A Good Laboratory Practice compliance statement was included.

F. CBI APPENDIX

None.